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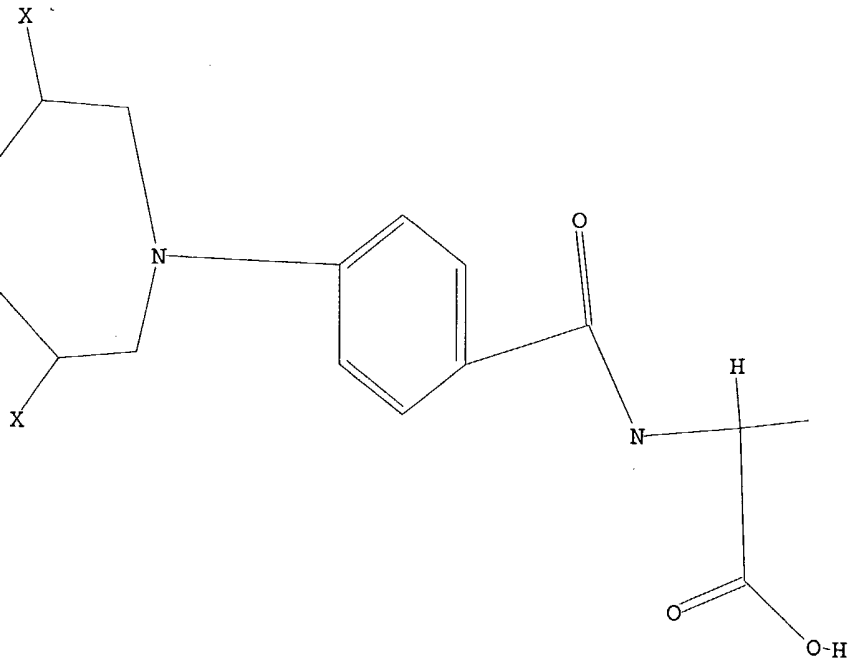

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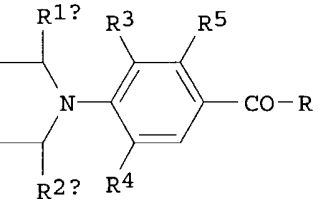
3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
CCESSION NUMBER: 2000:707131 CAPLUS
OCUMENT NUMBER: 133:267154
ITLE: Preparation of nitrogen mustard compounds and prodrugs
NVENTOR(S): Springer, Caroline Joy; Davies, Lawrence Christopher
ATENT ASSIGNEE(S): Cancer Research Campaign Technology Limited, UK
OURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
OCUMENT TYPE: Patent
ANGUAGE: English
AMILY ACC. NUM. COUNT: 1
ATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000058271	A1	20001005	WO 2000-GB1194	20000329
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000039746	A5	20001016	AU 2000-39746	20000329
NZ 513759	A	20010928	NZ 2000-513759	20000329
EP 1165493	A1	20020102	EP 2000-918981	20000329
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002540186	T2	20021126	JP 2000-607975	20000329
ORITY APPLN. INFO.:			GB 1999-7414 A	19990331
			WO 2000-GB1194 W	20000329

ER SOURCE(S): MARPAT 133:267154



I

Nitrogen mustard compds. and prodrugs I [R = OH or NHCH(Z)CO2R7, resp., where R1, R2 = Cl, Br, I, OSO2Me, or OSO2Ph; R1a, R2a, R1b, R2b = H, C1-4-alkyl or -haloalkyl; R3 = F, Cl, Br, I, OCHF2, C.tplbond.CH, OCF3, Me, CF3, SF5, SCF3, or CF2CF3; R4 = H, any group given for R3; R5 = H, F; R7 = H, Me3C, allyl; Z = (un)substituted -CH2-T-W, where T = CH2, O, S, S(O), or SO2; W = CO2H, CONH2, SO2NH2, SO3H, PO3H2, tetrazol-5-yl, heterocyclylthio, etc. (with provisos)] were prepared for use in therapy and treatment, for example, of cancer. Thus, [3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoyl]-L-glutamic acid, prepared via amidation of 3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoic acid with di-tert-butyl-L-glutamate hydrochloride, showed antitumor activity against breast carcinoma in mice at 0.98 mM vs. 2.9 mM for the prior art compound [3-fluoro-4-[bis(2-chloroethyl)amino]benzoyl]-L-glutamic acid.

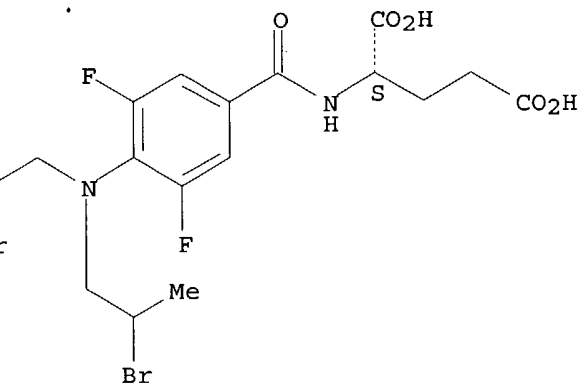
298211-06-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrogen mustard compds. and prodrugs)

298211-06-0 CAPLUS

L-Glutamic acid, N-[4-[bis(2-bromopropyl)amino]-3,5-difluorobenzoyl]- (9CI) (CA INDEX NAME)

olute stereochemistry.



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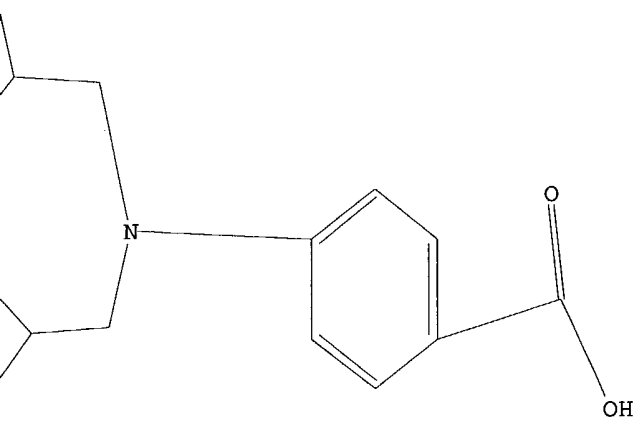

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6 L6 AND PY<1999

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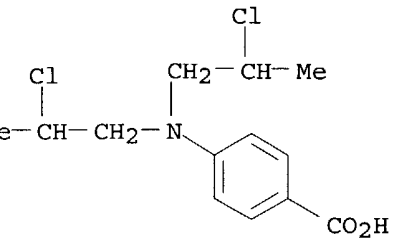
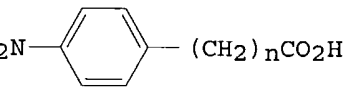
ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
CESSION NUMBER: 1979:167816 CAPLUS
CUMENT NUMBER: 90:167816
TLE: Some physicochemical properties and reactivity of p-[bis(2-chloroalkyl)amino]phenylalkanoic acids
THOR(S): Karpavicius, K.; Juodvirsis, A.; Prasmickiene, G.; Knunyants, I. L.
RPORATE SOURCE: Inst. Elementoorg. Soedin., Moscow, USSR
URCE: Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (**1979**), (1), 51-8
CODEN: IASKA6; ISSN: 0002-3353
CUMENT TYPE: Journal
NGUAGE: Russian
In p-(ClCHRCH2)2NC6H4(CH2)nCO2H (I; R = H, Me; n = 0-3) the cytotoxic

amino groups exhibit an appreciable electron-donating effect, whereas the carboxyalkyl groups show a weaker effect. The CH2 protons in the amino group of I (R = H; n = 1-3) are magnetically equivalent; those in I (R = H; n = 0) and the analogous cinnamic acid derivs. are not. The hydrolysis of C-Cl in I appears to be 1st order; that of I (R = Me) is an order of magnitude faster than that of I (R = H).

T **5379-46-4**
RL: PRP (Properties)
(NMR of)
N 5379-46-4 CAPLUS
N Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)



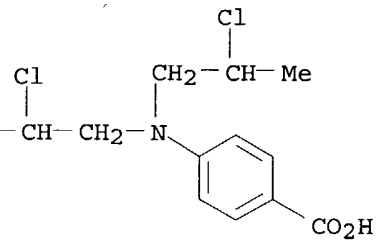
7 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
CCESSION NUMBER: 1978:58444 CAPLUS
OCUMENT NUMBER: 88:58444
ITLE: Physicochemical properties and antileukemia activity of some p-[bis(2-chloropropyl)amino]- and p-[bis(2-chloroethyl)amino]phenylalkanoic acid derivatives
UTHOR(S): Karpavicius, K.; Prasmickiene, G.; Juodvirsis, A.; Ivanova, L. E.; Khomchenovskii, E. I.
ORPORATE SOURCE: Inst. Biokhim., Vilnius, USSR
OURCE: Poiski Izuch. Protivoopukholevykh, Protivovospalitel'nykh Mutagennykh Veshchestv (**1977**), 66-75. Editor(s): Kanopkaite, S. Akad. Nauk Lit. SSR, Inst. Biokhim.: Vilnius, USSR. CODEN: 37BOA3
OCUMENT TYPE: Conference
ANGUAGE: Russian
I



I

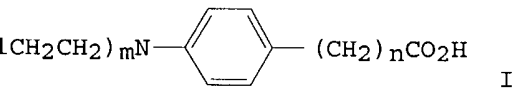
B The rate of hydrolysis, pKa, PMR spectra, LD50, and antileukemic effects of 8 p-[bis(2-chloroalkyl)amino]phenylalknoic acids (I) were presented. The 2-chloropropyl derivs. had a greater reactive capacity than did the 2-chloroethyl derivs. owing to the presence of the electron-donor Me group. The 2-chloropropyl derivs. were also generally more toxic than the 2-chloroethyl groups. The 2-chloropropyl derivs. were effective against granulocytopoiesis and on transplanted leukemias Nk/Ly and L-1210 in mice, whereas the 2-chloroethyl derivs. were effective against lymphopoiesis and development of Shchvetz leukemia in rats.

T **5379-46-4**
RL: BIOL (Biological study)
(antileukemic activity and physicochem. properties of)
N 5379-46-4 CAPLUS
N Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)



ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER:	1978:15944 CAPLUS
CUMENT NUMBER:	88:15944
TLE:	Comparative study of the general toxicity and antileukemic activity of new phenylalkanoic acid derivatives under experimental conditions
THOR(S):	Ivanova, L. E.; Zaretskii, I. I.; Khomchenovskii, E. I.; Karpavicius, K.; Prasmickiens, G.
RPORATE SOURCE:	Moscow, USSR
URCE:	Leikozologiya (**1975**), 4, 23-9 CODEN: LEIKDK
CUMENT TYPE:	Journal
NGUAGE:	Russian



I

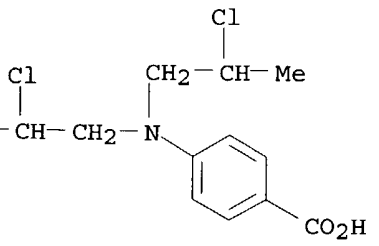
The toxicity and antileukemic effects of 8 phenylalkanoic acids (I) were determined The 2-chloropropyl derivs., p-di(2-chloropropyl)aminobenzoic acid [**5379-46-4**], p-di(2-dichloropropyl)aminophenylacetic acid [19521-09-6], p-di-(2-chloropropyl)aminophenylpropionic acid [22812-54-0], and p-di(2-chloropropyl) aminophenylbutyric acid [55774-31-7] had greater antileukemic effects than the resp. 2-chloroethyl derivs. although LD50 values tended to be lower.

5379-46-4

RL: BIOL (Biological study)
(leukemia inhibition by)

5379-46-4 CAPLUS

Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)



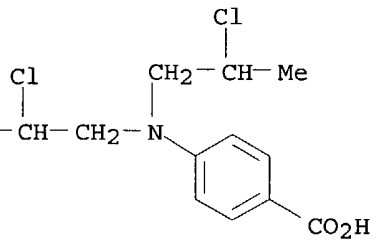
ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ESSION NUMBER:	1969:430178 CAPLUS
UMENT NUMBER:	71:30178
LE:	Synthesis and study of the reactivity of p-[bis(2-chloropropyl)amino]phenylalkanoic acids
HOR(S):	Prasmickiene, G.; Sukeliene, D.; Karpavicius, K.; Kil'disheva, O. V.

RPORATE SOURCE: Nauch.-Issled. Inst. Onkol., Vilnius, USSR
URCE: Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (**1969**), (3), 643-6
CODEN: IASKA6; ISSN: 0002-3353
CUMENT TYPE: Journal
NGUAGE: Russian

To 2.2 ml. POCl3 in Me2NCHO was added 5.72 g. p-(ClCHMeCH2)2NC6H4NH2 in the same solvent and the mixture kept 1 day at 40° to give p-(ClCH-MeCH2)2NC6H4CHO, (I), m. 104-6°. I with N2H4 gave the appropriate ylidenehyrazine, m. 167-9°, while HONH2 gave the oxime, m. 125-7°, which after 3 hrs. reflux in Ac2O gave 71% p-(ClCHMeCH2)2NC6H4CN, m. 128-30°, which heated in concentrated H2SO4 2 hrs. at 50° gave the corresponding amide, m. 138-40°. Oxidation of the aldehyde or heating the benzamide with HCl gave p-(ClCHMeCH2)2NC6H4CO2H, m. 160-2°. Propylene oxide added to p-H2NC6H4CH2CH2CONH2 in 30% AcOH gave, in 1 day, 77% (HOCHMeCH2)2NC6H4CH2CH2CONH2, m. 102-4°, which, heated with POCl3 1 hr., gave, on quenching in ice, 73% p-(ClCHMeCH2)2NC6H4CH2CH2CN (II), m. 66-8°, which in concentrated H2SO4 2 hrs. at 50° gave the corresponding amide, m. 58-60°. I heated with malonic acid in pyridine-piperidine 3 hrs. gave 76% p-(ClCHMeCH2)2NC6H4CH:CHCO2H (III), m. 131-3°. II heated with concentrated HCl gave 59% corresponding free acid, m. 69-71°, also formed by hydrogenation of III over PdCaCO3.

5379-46-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
5379-46-4 CAPLUS
Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)

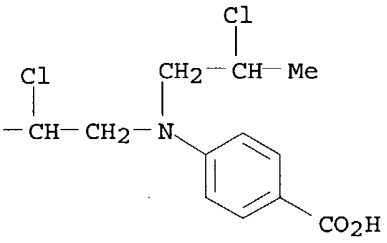


ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
CESSION NUMBER: 1966:84288 CAPLUS
CUMENT NUMBER: 64:84288
IGINAL REFERENCE NO.: 64:15785d-g
TLE: Tumor chemotherapy. XXX. Studies on the hexamethylenetetramine salt of p-bis(2-chloroethyl)amino-ω-bromoacetophenone
THOR(S): Jen, Yun-Feng; Kao, I-Sheng
RPORATE SOURCE: Inst. Mater. Med., Acad. Sinica, Shanghai, Peop. Rep. China
URCE: Huaxue Xuebao (**1965**), 31(6), 486-92,500
CODEN: HHHPA4; ISSN: 0567-7351
CUMENT TYPE: Journal
NGUAGE: Chinese

cf. CA 63, 17000b. p-(XRCHCH2)2NC6H4COCH2[(CH2)6N4]+Br- (Ia) (X = Br, R = H) (I), (X = I, R = H) (II), p-EtO2CNHC6H4COCH2[(CH2)6N4]+Br- (III), and p-EtO2CNHC6H4COCH2SC(:NH2+Br-)NH2 (IV), the analogs of the antitumor compound AT-584, were prepared The starting materials for the synthesis of I and II were p-bis[2-haloethyl (and propyl)] aminobenzoic acids (V and VI), resp. VI was synthesized by 2 methods: (1) [R(HO)CHCH2]2NC6H4CO2Et-p was first halogenated with PBr3 or POCl3 and then hydrolyzed with HCl or HBr to yield p-bis[2-chloropropyl (and 2-bromoethyl)] aminobenzoic acids. (2) Chlorination of p-bis(2-hydroxypropyl)aminobenzene with POCl3 in dimethylformamide gave p-bis(2-chloropropyl)aminobenzaldehyde, which was treated with KMnO4 in acetone to afford VI. The 2nd route gave a better yield. V and VI in benzene reacted sep. with SOCl2 to give the acid chlorides, which were treated sep. with diazomethane to yield the

diazoacetophenones (VII). VII were decomposed in dioxane with HBr to form bromoacetophenone derivs., which treated with hexamethylenetetramine in chloroform gave I and II, resp. p-Aminoacetophenone was treated with ethyl chloroformate in the presence of triethylamine as the condensing agent to form p-ethoxycarbonyliminoacetophenone (VIII). When N,N-diethylaniline was used as the condensing agent instead of triethylamine, the yield was better. VIII was first brominated in acetic acid with Br and then treated with hexamethylenetetramine or thiourea to afford III and IV, resp. Preliminary pharmacol. examns. showed that I and II were as active as AT-584 against HeLa cells in culture medium, while III and IV were less active.

5379-46-4, Benzoic acid, p-[bis(2-chloropropyl)amino]-
(preparation of)
5379-46-4 CAPLUS
Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)

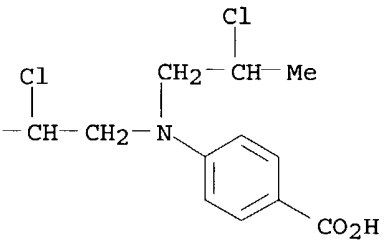


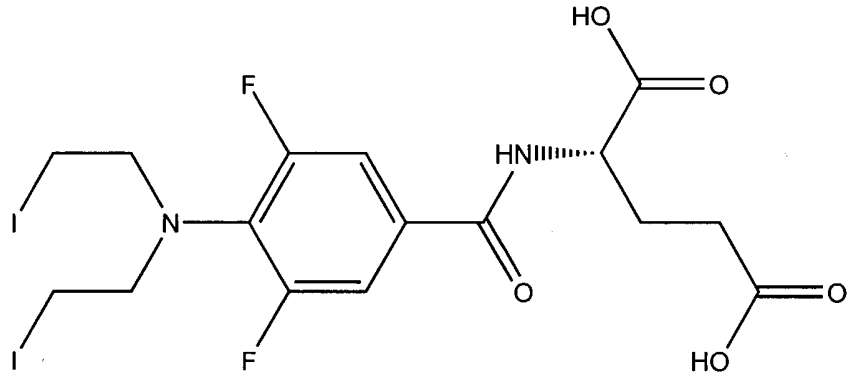
ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
CESSION NUMBER: 1951:863 CAPLUS
CUMENT NUMBER: 45:863
IGINAL REFERENCE NO.: 45:139h-i,140a-g
TLE: Aryl-2-haloalkylamines. VII. Some derivatives of 2-naphthyldi(2-haloalkylamines)
THOR(S): Davis, W.; Everett, J. L.; Ross, W. C. J.
RPORATE SOURCE: Roy. Cancer Hosp., London
URCE: Journal of the Chemical Society, Abstracts (**1950**) 1331-7
CODEN: JCSAAZ; ISSN: 0590-9791
CUMENT TYPE: Journal
NGUAGE: Unavailable

cf. C.A. 44, 6838i. This work is a continuation of that in C.A. 43, 7442g, and 44, 1431e, in which it was shown that many arylbis(2-haloalkyl)amines inhibited the growth of various animal tumors and of spontaneous and transmitted leukemia in the Furth AK 1 pure line; 2-C10H7N(CH2CH2Cl)2 has been used clinically for the treatment of various lymphadenopathies in human patients with encouraging results. 1,7-AcC10H6NH2 (16 g.), added to 11.2 g. NaOH and 18.4 g. 50% N2H4.H2O in 175 g. (HOC2H4)2O and heated 3 hrs. at 195°, gives 14.5 g. 1,7-EtC10H6NH2, brown oil (Ac derivative, m. 167°). 1,2,3,4-Tetrahydronaphthalene (264 g.), nitrated according to Schroeter (C.A. 16, 1673), gives 60 g. 5-NO2 and 45 g. 6-NO2 derivs.; catalytic reduction (Raney Ni) gives 5,6,7,8-tetrahydro-1- and -2-naphthylamines. 1-Keto-1,2,3,4-tetrahydronaphthalene oxime, reduced with Na in EtOH, gives 1,2,3,4-tetrahydro-1-naphthylamine, b10 114°. These amines were converted into the N,N-bis(2-hydroxyethyl) derivs. in the usual manner but it is preferable to use SOCl2 in CHCl3 for the chlorination stage, N,N-Bis(2-chloroethyl)-2-methyl-1-naphthylamine, oil. 1,2,3,4-Tetrahydro-N,N-bis(2-hydroxyethyl)-1-naphthylamine, m. 89° (picrate, m. 140°); N,N-bis-(2-chloroethyl)-1,2,3,4-tetrahydro-1-naphthylamine-HCl, m. 158°. 5,6,7,8-Tetrahydro-N,N-bis(2-hydroxyethyl)-1-naphthylamine picrate, m. 199° (decomposition); N,N-bis(2-chloroethyl)-5,6,7,8-tetrahydro-1-naphthylamine, an oil (picrate, m. 121°). N-(2-Naphthyl)-N-methyl-2-hydroxyethylamine picrate, m. 160°; N-(2-naphthyl)-N-methyl-2-chloroethylamine, m. 52.5° (inactive); N-(2-naphthyl)-N-methyl-2-hydroxypropylamine picrate, m. 154°; N-(2-naphthyl)-N-methyl-2-chloropropylamine, m. 64° (inactive). N,N-bis(2-hydroxyethyl)-6-methyl-2-naphthylamine,

m. 94°; N,N-bis(2-chloroethyl)-6-methyl-2-naphthylamine, m. 65°; bis(2-bromoethyl) analog, m. 88°; bis(2-iodoethyl) analog, m. 100-1°. N,N-Bis(2-chloroethyl)-8-methyl-2-naphthylamine, m. 63°; 8-Et homolog, m. 48°; bis(2-bromoethyl)-8-ethyl analog, m. 57°; bis(2-iodoethyl) analog, m. 85°. 8-Acetyl-N,N-bis(2-hydroxyethyl)-2-naphthylamine, yellow, m. 113°; bis(2-chloroethyl) analog, yellow, m. 84°; bis(2-bromoethyl) analog, yellow, m. 94.5° (solns. of the last 2 compds. exhibit an intense yellow-green fluorescence). N-(2-Chloroethyl)-1,2,3,4-tetrahydro-2-naphthylamine-HCl, m. 215°; picrate, m. 197°. N,N-Bis(2-chloroethyl)-1,2,3,4-tetrahydro-2-naphthylamine-HCl, m. 164°; bis(2-bromoethyl) analog-HBr, m. 229°. 5,6,7,8-Tetrahydro-N,N-bis(2-hydroxyethyl)-2-naphthylamine, m. 57°; bis(2-chloroethyl) analog, m. 65°, photoluminescent. N,N-Bis(2-hydroxyethyl)-2-phenanthrylamine, m. 155°; bis-(2-chloroethyl) analog, m. 91-2°; bis(2-bromoethyl) analog, m. 111-12°; bis(2-iodoethyl) analog, m. 117°. N,N-Bis(2-hydroxyethyl)-3-phenanthrylamine, m. 109-10°; bis(2-chloroethyl) analog, m. 73°; bis(2-bromoethyl) analog, m. 98°; bis(2-iodoethyl) analog, m. 125°. 2-(2-Hydroxyethylamino)fluorene, yellow, m. 150° (cf. C.A. 43, 7442g); 2-chloroethyl analog, m. 127°. 2-[Bis(2-bromoethyl)amino]fluorene m. 137°. N'-Propionyl-N,N-bis(2-chloroethyl)-p-phenylenediamine m. 101-3°. p-[Bis(2-chloropropyl)amino]benzoic acid, m. 165-6°; Me ester, m. 61°. p-MeOC6H4N(CH2CH2Cl)2 (2.5 g.) and 3.4 g. Et2NCS2Na in 200 ml. 50% aqueous Me2CO, refluxed 2 hrs., give N,N-bis[2-(diethyldithiocarbamyl)ethyl]-p-anisidine, m. 85-6°. p-MeOC6H4[NCH2CH(OH)CH2Cl]2 (40 g.) in 500 ml. boiling ether, gradually treated with 40 g. KOH, gives N,N-bis(2,3-epoxypropyl)-p-anisidine, yellow, b9 228-9°; this is inactive. Data are given for the rate of hydrolysis of a number of these compds. in 50% aqueous Me2CO at 66°. The effect of various substituents is discussed. There is the expected increase in the rate of hydrolysis on passing from the Cl to Br compound but a somewhat surprising decrease for the iodides.

5379-46-4, Benzoic acid, p-[bis(2-chloropropyl)amino]-
(preparation of)
5379-46-4 CAPLUS
Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)





[3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoyl]-l-glutamic acid